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(54) Title: PHARMACEUTICAL COMPOSITIONS HAVING THE SHAPE OF POWDERS OF CROSS–LINKED POLYMERS LOADED WITH DRUGS AND RELATED PREPARATION PROCESS BY SUPERCRITICAL FLUIDS

(57) Abstract

Pharmaceutical compositions in powder form are prepared by loading drugs solubilized in supercritical fluids on cross–linked polymers. The loading process is carried out by means of two steps. In the first step the supercritical fluid is saturated with the drug in suitable temperature and pressure conditions. In the second step the supercritical fluid containing the drug is contacted with the cross–linked polymer. Owing to its particular properties the supercritical fluid penetrates into the polymer and allows the drug to impregnate the polymer itself. After the removal of the fluid the drug remains in the polymer itself.

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PHARMACEUTICAL COMPOSITIONS HAVING THE SHAPE OF POWDERS OF CROSS-LINKED POLYMERS LOADED WITH DRUGS AND RELATED PREPARATION PROCESS BY SUPERCRITICAL FLUIDS

FIELD OF THE INVENTION

The present invention refers to pharmaceutical compositions in powder form consisting of active substances loaded on cross-linked polymers prepared with the technology of the supercritical fluids.

PRIOR ART

The technology with supercritical fluids (V. Krukonis, Proc. III International Symposium on Supercritical Fluids, Strasbourg, Vol. 1,1, 1994; Proceedings IV International Symposium on Supercritical Fluids, Sendai (Japan), May, 11-14, 1997, S. Sato and K. Arai Eds.) is notably developing owing to the particular properties of these fluids which allow a safer use of them instead of the normal organic solvents even in the pharmaceutical field (K. A. Larson, M. L. King, Biotechnol. Prog., 3, 73, 1986) in the operations of extraction and purification (G. Brunner, "Gas Extraction", Springer, Darmstadt, 1994).

Besides for these applications the properties of the supercritical fluids may be exploited in the processing of the materials allowing, for example, the production of powders having controlled granulometry (J. W. Tom, P. G. Debenedetti, J. Aerosol. Sci., 22, 555, 1991).

Among the processed materials a particular attention has been devoted to the polymeric materials, both for the production of micronized powders and for their fractionation (M. McHugh, V. Krukonis, "Supercritical Fluid Extraction", Butterworth, Meinemann, 1994). Another particularly interesting aspect consists of the utilization of the technology with supercritical fluids for the loading of essentially linear polymers, with additives (C. A. Perman et al., US Patent 5,508,060; M. L. Sand, US Patent 4,598,006). In particular the importance of the absence of cross-linking in the polymer is pointed out (M. L. Sand, US Patent 4,598,006) in order to allow the operation of impregnation.

Unexpectedly, using cross-linked polymers we succeeded to load them, reaching reasonable loading levels, with drugs, in presence of supercritical fluids.

SUMMARY

The present invention refers to pharmaceutical compositions in powder form

prepared by loading drugs solubilized in supercritical fluids on cross-linked polymers.

Said compositions are prepared by:

1) solubilization of the drug in a supercritical fluid;

2) contacting the supercritical fluid containing the solubilized drug with the cross-linked polymer;

3) impregnation of the cross-linked polymer with the supercritical fluid containing the drug;

4) removal of the supercritical fluid with consequent loading of the drug in the cross-linked polymer itself.

DETAILED DESCRIPTION OF THE INVENTION

The fluid, consisting of a pure component or mixture, by a pump is taken to the desired pressure conditions. It is sent to a first container and from this one it is passed through a heat exchanger in order to take it to temperature and pressure conditions higher than those at which it can be considered as supercritical. For example, in the case of pure components, carbon dioxide (CO_2) is taken to conditions higher than 31°C and 73.8 bar; ethylene higher than 9°C and 54.4 bar; methane higher than –82°C and 46.0 bar; propylene higher than 92°C and 46.2 bar; nitrous oxide (N_2O) higher than 36.4°C and 72.45 bar, in the case of a mixture of carbon dioxide (CO_2) mixed with methanol (7%) it is taken to conditions above 40°C and 80 bar. The supercritical fluid is then passed through an extractor containing the drug. At the outlet of the extractor the supercritical fluid stream, consisting of a pure component or mixture, containing certain amount of drug which solubilized at the temperature and pressure conditions fixed in advance, is contacted in a reactor practically set to the same operative conditions, with the polymer, according to a static or a dynamic process. In the static case a predeterminate volume of the supercritical fluid with the solubilized drug is introduced in an adequate container and left to equilibrate with an adequate quantity of polymer, for a contact time in the range between 5 minutes and 72 hours, preferably between 0.25 hours and 24 hours; this equilibration loading step can be repeated if necessary more times. In the case of the dynamic process the stream of the supercritical fluid generated by the pump, at the outlet of the extractor, is passed through a column, of predetermined size and length,

containing the polymer, for a contact time between 5 minutes and 72 hours, preferably between 0.25 hours and 24 hours. Said process embodiments, static and dynamic, can be combined; for example after passing dynamically a given volume of supercritical fluid with the solubilized drug through a column of predetermined sizes, the stream is stopped, the supercritical fluid is left in static contact with the polymer for a predetermined time and subsequently the stream of the supercritical fluid is passed again through the column. In both the processes the loading of the drug occurs essentially through the effect of the partitioning of the drug itself between the supercritical fluid and the polymer. This stage of the operation may be if necessary aided by acting on other factors assisting the release of the drug from the supercritical fluid. At the outlet from the impregnation reactor the fluid stream is passed through an absorber containing activated carbon or other material suitable to remove from the stream itself any trace of the, in case residual, drug. The fluid stream may then be brought back to the ambient conditions and drained or if necessary cooled, sent to a reflux receiver and from this one by the pump to the extractor.

The polymers according to the present invention are cross-linked hydrophilic and hydrophobic polymers. Among the cross-linked polymers we can mention, as an however not exhaustive exemplification: the cross-linked polyvinyl pyrrolidone, the cross-linked sodium carboxymethyl cellulose and cross-linked sodium starch glycolate, among the hydrophilic ones; the cross-linked polystyrene, the cross-linked acrylic acid and the sodium salt of cross-linked polymethyl methacrylate among the hydrophobic ones.

Among the drugs which may be formulated according to the invention we may mention, as an however not exhaustive exemplification:

Analgesics and non steroidal antiinflammatories and their salts: sodium diclofenac, ibuprofen, naproxen, etc.; antibactericals: amoxicillin, cephalosporins, etc.; antifungals and antipsoriatics: ketoconazole, griseofulvin, itraconazole, thioconazole, etc.; antivirals: acyclovir, gancyclovir, etc.; antineoplastics and immunosuppressives: ciclosporin, etoposide, taxole and derivatives, etc.; anxiolytics, sedatives, hypnotics: lorazepam, oxazepam, temazepam, etc.; sexual hormones: medroxyprogesterone acetate, testosterone, estradiol, progesterone, etc.; peptidic molecules having different activity: LH-RH analogues, calcitonins,

glutathione.

The compositions according to the present invention, contain from 0.1 to 99.9% and preferably from 0.1 to 50% by weight of the active principle with respect to the polymer.

The compositions are formulated as packets or as tables, perles pellets or granules for pharmaceutical use.

EXAMPLES

For the illustrative aim of the invention the following examples are reported hereinafter:

Example No. 1

5 grams of polymer, cross-linked polyvinyl pyrrolidone, placed in a column of 50 cm length and 0.6 cm size, are contacted with CO_2 saturated with nimesulide at 160 bar and 60 C°. The flux of the incoming stream of saturated CO_2 expressed in flow of liquid CO_2 is equal to 0.1 litres/minute. At the end of the test, after 8 hours, the polymer turns out to be impregnated of nimesulide for an amount equal to 24.47%.

Example No. 2

5 grams of polymer, cross-linked polymethyl methacrylate, placed in a column of 50 cm length and 0.6 cm size, are contacted with CO_2 saturated with acyclovir at 220 bar and 50 C°: the flux of the incoming stream of saturated CO_2 expressed in flow of liquid CO_2 is equal to 0.1 litres/minute.

At the end of the test, after 24 hours, the polymer turns out to be impregnated of acyclovir for an amount equal to 21.2%.

Examples No. 3-6

15 grams of polymeric materials (respectively physically cross-linked polyvinyl pyrrolidone, chemically cross-linked polyvinyl pyrrolidone, cross-linked sodium starch glycolate and acrylic acid cross-linked with allilic esters of sucrose) are put into a 200 ml reactor and contacted with CO_2 saturated with the drug.

The reactor is washed first with CO_2 and then a stream of CO_2 saturated with different drugs (nimesulide, ketoprofen, piroxicam, cimetidine respectively) is introduced at 160 bar and 60 °C.

At the end of the tests, after contact times respectively of 0.5 hour, 0.25 hour, 1

hour, 2 hours, the concentrations of drug in the polymers are 22.2; 25.6; 15.3; and 20.4% respectively.

CLAIMS

1. Pharmaceutical compositions in form of powders consisting of cross-linked polymers loaded with active principles by an impregnation process with supercritical fluids.

2. Compositions as claimed in claim 1, characterized in that said active principles are present in the powders of the cross-linked polymers in an amount ranging from 0.1 to 99.9% by weight, preferably in an amount from 0.1 to 50% by weight with respect to the polymers.

3. Compositions as claimed in claim 1, characterized in that said cross-linked polymers comprise hydrophilic cross-linked polymers such as the cross-linked polyvinyl pyrrolidone, the cross-linked sodium starch glycolate, the cross-linked sodium carboxymethyl cellulose.

4. Compositions as claimed in claim 1, characterized in that said cross-linked polymers comprise hydrophobic cross-linked polymers such as the cross-linked polystirene, the cross-linked acrylic acid or the cross-linked polymethyl methacrylate sodium salt.

5. Compositions as claimed in claim 1, characterized in that said powders are formulated as packets or as tablets, perles, pellets or granules for pharmaceutical use.

6. Process for the preparation of pharmaceutical compositions as defined in claim 1, characterized by: 1) solubilization of the drug in a supercritical fluid; 2) contacting the supercritical fluid containing the solubilized drug with the cross-linked polymer; 3) impregnation of the cross-linked polymer with the supercritical fluid containing the drug; 4) removal of the supercritical fluid with consequent loading of the drug in the cross-linked polymer itself.

7. Process as claimed in claim 6, characterized in that said contacting step is carried out by a static or a dynamic embodiment.

8. Process as claimed in claim 6, characterized in that said contacting step is carried out by a contact time from 5 minutes to 72 hours.

9. Process as claimed in claim 6, characterized in that said contacting step is carried out by a contact time from 0.25 hours to 24 hours.

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	ZIA, HOSSEIN ET AL: "Comparison of nasal insulin powders prepared by supercritical fluid and freeze-drying techniques" PART. SCI. TECHNOL. (1997), 15(3), 217-244 CODEN: PTCHDS;ISSN: 0272-6351, XP002103767 see page 275 - page 276 ---	1,2,4-7
X	US 5 128 142 A (MULLIGAN SEAMUS ET AL) 7 July 1992 see column 4 - column 5; example 2 ---	1-3,5
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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